**SUPPLEMENTARY APPENDIX**

**Supplementary Table 1. Variables included in each frailty domain of the HFA-ESC 2019 definition and in the frailty index.**

|  |  |
| --- | --- |
| **HFA-ESC 2019 frailty domains\*** | **Frailty index°** |
| **Clinical domain**1) At least 3 comorbidities among hypertension, dyslipidemia, diabetes mellitus, peripheral artery disease, prior stroke or transient ischemic attack, history of atrial fibrillation, history of myocardial infarction, previous valve surgery, chronic obstructive pulmonary disease, chronic kidney disease, history of cancer2) Falls3) Cardiac cachexia | Hypertension |
| Dyslipidemia |
| Diabetes |
| Peripheral artery disease |
| Prior cerebrovascular event |
| Prior atrial fibrillation |
| Prior myocardial infarction |
| Previous PCI or CABG |
| Chronic obstructive pulmonary disease |
| Chronic kidney disease |
| History of cancer |
| Depressive disorder |
| Dementia |
| **Social domain**1) Absence of caregiver2) Institutionalized | ADL or IADL impairment |
| Inability to perform exercise |
| Cardiac cachexia |
| Implantable device |
| Previous valve interventions |
| **Psycho-cognitive domain**1) Depressive disorder2) Cognitive impairment or dementia | BMI >30 or <18 |
| LVEF <50% |
| Thromobocytopenia or thromobocytosis |
| Hypo/hyperkalemia |
| Hypo/hypernatremia |
| **Functional domain**1) ADL or IADL impairment2) Balance disturbances3) Inability to perform exercise | TAPSE<18 mm |
| Hemoglobin <9 g/L or >18 g/L |
| Severe tricuspid regurgitation |
| Severe mitral regurgitation |
| Falls |
| >1 HF hospitalization in the last year |
| SBP at inclusion >130 or <90 mmHg |

\*Each domain is satisfied if at least one item is present.

**°**Each variable gives 1 point if satisfied. The frailty index is calculated as the ratio between the actual variables present and all the variables considered (range from 0 to 1)

**Supplementary Table 2. Impact of the number of frailty domains fulfilled on clinical outcomes, after multivariable adjustment for GDMT prescription.**

|  |  |  |
| --- | --- | --- |
|  | **HR (95% CI)** | **p-value** |
| **All-cause death** | 1.67 (1.42 – 1.97) | <0.001 |
| **CV death** | 1.71 (1.41 – 2.09) | <0.001 |
| **First HFH** | 1.20 (1.03 – 1.40) | 0.020 |
| **All-cause death or HFH** | 1.40 (1.2 – 1.59) | <0.001 |

HR are presented for each domain increase and adjusted for prescription of 50% target doses of beta-blockers, ACE-I/ARB/ARNI and mineralcorticoid receptor antagonists. Sub-hazard ratios are presented for HFH. CI = confidence interval; CV = cardiovascular; GDMT = guideline directed medical therapy; HFH = heart failure hospitalization; HR = hazard ratio

**Supplementary Table 3. Impact of the number of frailty domains fulfilled on clinical outcomes, after multivariable adjustment for known modifiers.**

|  |  |  |
| --- | --- | --- |
|  | **HR (95% CI)** | **p-value** |
| **All-cause death** | 1.45 (1.22 – 1.74) | <0.001 |
| **CV death** | 1.47 (1.19 – 1.81) | <0.001 |
| **First HFH** | 1.17 (0.99 – 1.38) | 0.073 |
| **All-cause death or HFH** | 1.27 (1.11 – 1.45) | <0.001 |

HR are presented for each domain increase and adjusted for known modifiers (All-cause death: *fulfillment of the HFA-ESC definition of advanced HF, age, sex, inpatient versus outpatient status, New York Heart Association class III–IV, systolic blood pressure, heart rate and estimated glomerular filtration rate*; CV death*: fulfillment of the HFA-ESC definition of advanced HF, age, sex, inpatient versus outpatient status, New York Heart Association class III–IV, left ventricular ejection fraction <40%, systolic blood pressure, heart rate and estimated glomerular filtration rate*; First HFH: *fulfillment of the HFA-ESC definition of advanced HF, age, sex, history of atrial fibrillation, chronic obstructive pulmonary disease, New York Heart Association class III–IV, left ventricular ejection fraction <40% and estimated glomerular filtration rate;* all-cause death or HFH: *fulfillment of the HFA-ESC definition of advanced HF, age, sex, inpatient versus outpatient status, New York Heart Association class III–IV, systolic blood pressure and estimated glomerular filtration rate*). Sub-hazard ratios are presented for HFH.

CI = confidence interval; CV = cardiovascular; GDMT = guideline directed medical therapy; HFH = heart failure hospitalization; HR = hazard ratio

**Supplementary** **Table 4. Impact of each frailty domain on clinical outcomes at multivariable analysis.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All-cause death** | **CV death** | **First HFH** | **All-cause death or HFH** |
|  | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **SHR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Clinical domain** | 1.43 (1.01 - 2.04) | **0.043** | 1.51 (0.99 - 2.30) | **0.053** | 1.36 (0.97 - 1.89) | 0.071 | 1.35 (1.04 – 1.74) | **0.023** |
| **Functional domain** | 2.77 (1.75 - 4.39) | **<0.001** | 3.27 (1.85 – 5.78) | **<0.001** | 1.42 (0.98 – 2.04) | 0.062 | 1.83 (1.36 – 2.46) | **<0.001** |
| **Social domain** | 1.31 (0.96 - 1.79) | 0.092 | 1.45 (1.01 - 2.09) | 0.46 | 1.23 (0.91 - 1.67) | 0.17 | 1.26 (0.99 - 1.60) | 0.057 |
| **Psycho-cognitive domain** | 1.75 (1.29 - 2.37) | **<0.001** | 1.62 (1.13 - 2.33) | **0.009** | 0.95 (0.68 - 1.33) | 0.77 | 1.35 (1.06– 1.73) | **0.015** |

In the multivariable models, each domain is adjusted for all other three domains. CI = confidence interval; CV = cardiovascular; HFH = heart failure hospitalization; HR = hazard ratio; SHR = subhazard ratio

**Supplementary Table 5. Comparison between adjusted hazard ratios evaluating the independent prognostic impact of each individual domain on all-cause death.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Clinical**  | **Functional**  | **Social**  | **Psycho-cognitive**  |
| **Clinical**  |  | **0.03** | 0.69 | 0.44 |
| **Functional**  | **0.03** |  | **0.004** | 0.12 |
| **Social**  | 0.69 | **0.004** |  | 0.17 |
| **Psycho-cognitive**  | 0.44 | 0.12 | 0.17 |  |

Data are presented as p-values derived from a formal test of equality. Each adjusted HR (for a specific frailty domain) was compared with all other adjusted HRs (for all other individual frailty domains). Overall p-value (for global differences between all adjusted HRs) is 0.026.

**Supplementary Table 6. Comparison between adjusted hazard ratios evaluating the independent prognostic impact of each individual domain on CV death.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Clinical**  | **Functional**  | **Social**  | **Psycho-cognitive**  |
| **Clinical**  |  | **0.039** | 0.88 | 0.82 |
| **Functional**  | **0.039** |  | **0.01** | **0.05** |
| **Social**  | 0.88 | **0.01** |  | 0.65 |
| **Psycho-cognitive**  | 0.82 | **0.05** | 0.65 |  |

Data are presented as p-values derived from a formal test of equality. Each adjusted HR (for a specific frailty domain) was compared with all other adjusted HRs (for all other individual frailty domains). Overall p-value (for global differences between all adjusted HRs) is 0.08

**Supplementary Table 7. Comparison between adjusted hazard ratios evaluating the independent prognostic impact of each individual domain on first HFH.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Clinical**  | **Functional**  | **Social**  | **Psycho-cognitive**  |
| **Clinical**  |  | 0.88 | 0.66 | 0.14 |
| **Functional**  | 0.88 |  | 0.51 | 0.15 |
| **Social**  | 0.66 | 0.51 |  | 0.25 |
| **Psycho-cognitive**  | 0.14 | 0.15 | 0.25 |  |

Data are presented as p-values derived from a formal test of equality. Each adjusted SHR (for a specific frailty domain) was compared with all other adjusted SHRs (for all other individual frailty domains). Overall p-value (for global differences between all adjusted SHRs) is 0.39.

**Supplementary Table 8. Comparison between adjusted hazard ratios evaluating the independent prognostic impact of each individual domain on all-cause death or HFH.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Clinical**  | **Functional**  | **Social**  | **Psycho-cognitive**  |
| **Clinical**  |  | 0.14 | 0.69 | 0.97 |
| **Functional**  | 0.14 |  | **0.03** | 0.15 |
| **Social**  | 0.69 | **0.03** |  | 0.66 |
| **Psycho-cognitive**  | 0.97 | 0.15 | 0.66 |  |

Data are presented as p-values derived from a formal test of equality. Each adjusted HR (for a specific frailty domain) was compared with all other adjusted HRs (for all other individual frailty domains). Overall p-value (for global differences between all adjusted HRs) is 0.20.

**Supplementary Table 9. Impact of frailty index on clinical outcomes.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All-cause death** | **CV death** | **First HFH** | **All-cause death or HFH** |
|  | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **SHR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Frailty index** | 1.75 (1.52 – 2.02) | <0.001 | 1.80 (1.51 – 2.13) | <0.001 | 1.28 (1.23 – 1.47) | <0.001 | 1.51 (1.36 – 1.68) | <0.001 |

HR and SHR are showed per 0.1 increase in frailty index. CI = confidence interval; CV = cardiovascular; HFH = heart failure hospitalization; HR = hazard ratio; SHR = subhazard ratio

**Supplementary Figure 1. Frailty index distribution.**



**Supplementary Figure 2. Additional clinical outcomes stratified by (A) the number of frailty domains fulfilled or (B) frailty quintiles.**

****A. Kaplan-Meyer curves showing the impact of the number frailty domains on cardiovascular death and HF hospitalizations. B. Kaplan-Meyer curves showing the impact of the frailty quintiles on cardiovascular death and HF hospitalizations.

HF = heart failure.